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Infliximab Therapeutic Drug Monitoring in Inflammatory Bowel Disease Virtual Biologics Clinic Leads to Durable Clinical Results

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Abstract

Background: Therapeutic drug monitoring (TDM) of infliximab (IFX) trough levels and anti-drug antibodies in conjunction with symptoms, disease history, and investigations can aid decision-making. This study evaluated 1-year outcomes of patients with decisions that were altered on the basis of TDM results, in order to investigate whether outcomes from TDM-based decisions to adjust or stop IFX treatment are durable. ***Methods:*** We retrospectively collected clinical outcomes 12 months post treatment decisions based on proactive TDM. Patients whose initial treatment decisions were altered on the basis of TDM results were compared with those where the decision remained unchanged. Events of interest were inpatient admissions with active inflammatory bowel disease (IBD), further changes to biologic therapy, and IBD-related health-care costs. ***Results:*** Of 189 patients, 54 (28%) had initial treatment decisions altered in the light of TDM results. The 135 patients whose initial decision was not altered in light of TDM results served as the comparator. There were no differences in hospitalization rates or subsequent biologic switches between the altered decision groups and the comparator group. IBD-related health-care costs were higher in those whose initial decision was altered (median GBP 7,912 vs. GBP 6,521; $p < 0.0001$) due to higher drug costs (median GBP 7,062 vs. GBP 6,012; $p < 0.0001$). ***Conclusion:*** Our study demonstrates good outcomes from changes to IFX treatment based on TDM. Patients with a decision to stop, switch, or continue with an adjusted IFX dose experienced comparable clinical outcomes but had higher drug-related expenditure than those whose treatment decision was not altered in light of TDM.

Introduction

Advances in the treatment of inflammatory bowel disease (IBD) have led to the widespread use of biologic therapies [1]. The most commonly used biologics include the TNF-α inhibitors infliximab (IFX) and adalimumab, with increasing use of more recent biologic agents including vedolizumab and ustekinumab [1]. Although up to 85% of patients with IBD show clinical response to the TNF-α inhibitors, initial non-response (primary non-response) or a subsequent loss/reduced clinical response (secondary loss of response) remains a challenge [2–4]. In addition, approximately 5% of patients experience infusion-related reactions [4]. These scenarios present physicians

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with difficult management decisions. Although anti-TNF-α therapy may reduce costs from hospitalizations and health-care encounters, overall drug costs are high [5].

The ability to predict response to anti-TNF-α therapy more accurately and optimize dosing regimens could reduce long-term costs and achieve remission in a greater proportion of patients. Therapeutic drug monitoring (TDM) of IFX trough levels and anti-drug antibodies (ADAs) can aid decision-making, but the role of TDM in routine clinical practice remains poorly defined [6–9]. The use of IFX trough levels along with ADAs provides key insights into the likely response, or lack thereof, to anti-TNF-α therapies [10]. Although there is good evidence that secondary loss of response is best managed with the aid of TDM [11], the role of proactive TDM to guide decision-making remains more controversial [11, 12]. A randomized controlled trial failed to demonstrate clinical benefits, but optimization of TDM prior to randomization may have led to negative results or a type II statistical error may have occurred [9].

In addition, despite the availability of biosimilars, IFX remains far more expensive, than traditional treatment options. In a previous study, we demonstrated that among 191 patients, IFX trough levels were frequently outside the therapeutic range in almost 50% of patients, and ADAs were present in 30.4% [13]. Treatment decisions were changed in the light of knowledge of the results of TDM in 29% of cases [13].

The aim of the current study was to evaluate the 12-month clinical outcomes and health-care costs of patients who had their initial treatment decision altered based on knowledge of TDM results, compared with patients where the initial treatment decision remained the same, even when the results of TDM were known. Some clinicians are not convinced that TDM contributes to the management of patients in clinical remission and have expressed potential concerns over altering IFX treatment based on results of TDM. Patients who are in clinical remission with an unfavourable TDM profile of low trough levels and high ADAs who stop IFX could, in theory, be at higher risk of disease recurrence (hospitalization or subsequent switch to another biologic agent). Additionally, patients experiencing active inflammation with an unfavourable TDM profile of low trough levels and high ADAs are at high risk of IFX treatment failure [10, 14]. Switching these to an alternative anti-TNF will likely improve their clinical status but could again in theory worsen their clinical outcomes. We therefore aimed to demonstrate that those patients whose initial treatment decisions were altered did not experience a higher rate of disease deterioration. On the assumption that clinical decision-making based on proactive TDM ensures all patients are on appropriate medical therapy, our a priori hypothesis was that there would be no difference in clinical outcomes between the groups whose initial treatment decision was altered based on the knowledge of results of TDM and the group where the treatment decision was not altered.

Methods

The current study provides 12-month follow-up data in a cohort of patients previously described [13]. Initially, patients with IBD established on IFX were reviewed in a virtual biologics clinic during 2016–2017. Virtual biologics clinics are used at our institution to review every patient on a biologic therapy remotely on annual basis. Decisions to continue, stop, adjust, or switch biologic therapy are taken by a team of gastroenterologists and IBD specialist nurses. This multidisciplinary team (MDT) initially made blinded treatment decisions, without the knowledge of each patient's TDM results, and based only on routine clinical information, including recent outpatient clinic reviews, biochemistry, and imaging and/or endoscopy results. This first decision was then recorded. The results of TDM were then made available to the MDT, and a second decision, incorporating these results, was then recorded, which may have been altered in the light of the TDM results. The following TDM-based treatment algorithm was applied (Fig. 1). Patients in clinical response/remission with trough levels in range and no or low ADAs continued at previous dose and interval, while those in clinical remission with low trough levels and high ADAs stopped IFX therapy. Those in clinical response/remission with low trough levels and no or low ADAs had their dosing intensified, while in those with high trough levels dosing was decreased. Patients with active symptoms and inflammation with low trough levels and high ADAs were switched to an alternative anti-TNF, while those patients with active symptoms and inflammation having normal trough levels were switched to a non-anti-TNF biologic. For 54 patients, the initial decision was altered based on the results of TDM. Subsequent TDM measurements were taken proactively after a further 2 infusions for patients whose IFX dosing or frequency was altered, or reactively if a loss of response occurred. This study is a 12-month follow-up subsequent to these virtual biologic clinical decisions using retrospectively collected data. All TDM in the initial study was based on proactive testing of the whole IFX cohort using a drug-sensitive assay as previously described when TDM first became available to our service [13].

Data Collection

We collected data concerning the 12-month clinical and economic impacts of the final decisions, in light of results of TDM, made in the MDT. In order to achieve this, all encounters with the IBD service (outpatient clinical appointments, IBD helpline contacts, and inpatient admissions), IBD-related investigations (endoscopy or cross-sectional imaging), and biologic drug administration data were extracted from the hospital's electronic patient record. As follow-up was in the year 2016–2017, all prices for IBD

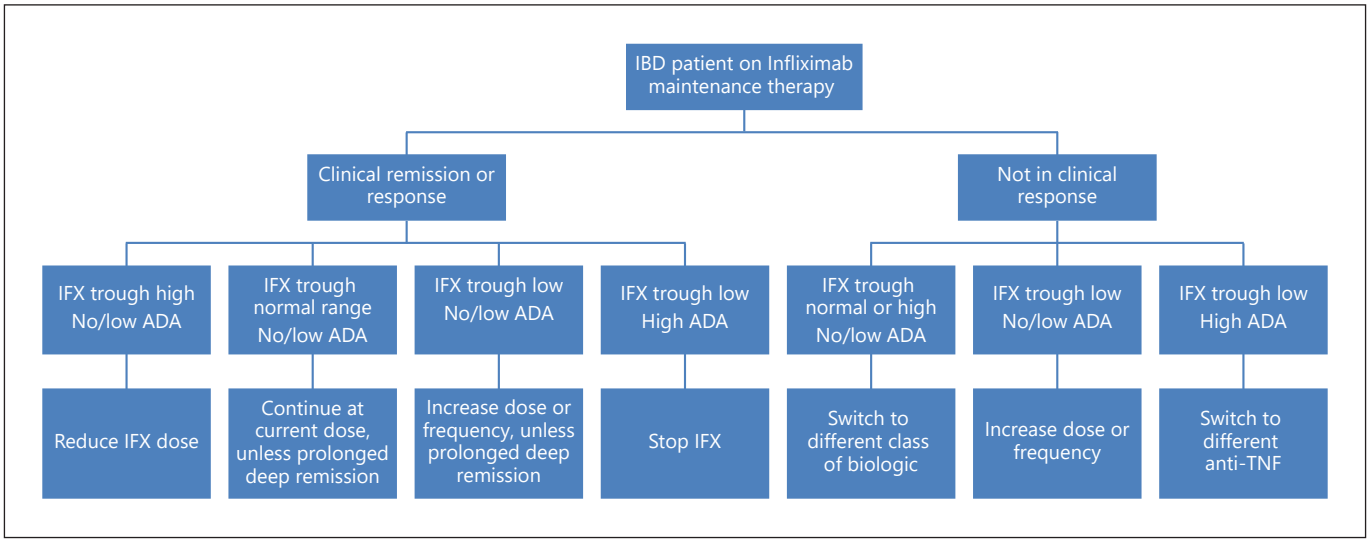

Fig. 1. Treatment algorithm for IFX based on TDM. IFX, infliximab; TDM, therapeutic drug monitoring; IBD, inflammatory bowel disease; ADA, anti-drug antidody.

service encounters and investigations were based on 2016 NHS reference pricing. Costs for biologic drugs were obtained from the hospital pharmacy, and the costs of day-case administration of intravenous preparations, provided by the hospital finance team, were added to these. For the year 2016–2017, the IFX biosimilar CT-P13 was used routinely, while adalimumab, vedolizumab, and ustekinumab were used as originator products. Medication prices have substantially changed since 2016 in the UK, and to give an accurate picture of the costs that are now applicable, a further analysis of costs as applicable in 2020 was performed.

Outcomes and Analysis

The primary outcome of interest was the clinical course in the group where the first decision was altered based on the results of TDM ("change" group) versus the group of patients where the decision was unaltered ("no change" group) despite subsequent knowledge of TDM results. For this, we defined inpatient admissions and/or the need for a subsequent switch in biologic therapy as relevant clinical events. Secondary outcomes included the overall health-care costs of the change group compared with the no change group. We also conducted subgroup analyses, where we divided the change group and no change groups into 4 subgroups: IFX stopped (I), IFX switched to an alternative biologic (II), IFX continued with an adjusted dose or interval (III), and IFX continued at same dose and interval (IV).

Data were first presented in a descriptive manner. Categorical data were analysed using a χ^2 test. Continuous data were analysed with *t* tests for normally distributed, and Mann-Whitney test for non-normally distributed, continuous variables. Not all treatment decisions made within the MDT were implemented by the responsible clinicians. Data were therefore analysed based on whether the MDT's decision was actually implemented (analogous to a per protocol analysis used in clinical trials). Analyses based on the MDT's decision, irrespective of whether it was implemented (analogous to an intention-to-treat (ITT) analysis), were also conducted. Statistical significance was set at 1%, and the analysis was performed with SPSS version 22 (SPSS Inc., Chicago, IL, USA). As a clinical audit using routinely collected clinical data, this study is exempt from the need for ethics committee approval [15].

Results

Of 191 patients included in the previous study, 4 were excluded as patient records were unavailable. A total of 187 (55% men, age range 18–86 years [mean 40 years, standard deviation 14]) patients were therefore included in this study. In total, 53 (28.3%) patients had their initial treatment decision altered following knowledge of TDM results. A total of 134 (71.6%) patients initial treatment decisions remained unaltered after knowledge of TDM results. Details of the treatment decisions made were previously published [13]. Over 80% of MDT-recommended decisions altered in light of knowledge of results of TDM were instigated by the responsible clinician.

Primary Outcome as per Implemented Decision

There were no differences in the primary clinical outcomes between the change and no change groups. In 53 patients with a decision that was altered based on the results of TDM, 3 inpatient admissions (5.7%) occurred, compared with 15 (11.1%) in the no change group (p = 0.40). The rate of subsequent biologic switches was 1 (1.9%) in the change and 2 (1.5%) in the no change group

(p = 1.00). There were no significant differences in the percentage of patients requiring imaging investigations (27.7 vs. 31.8%; p = 0.73) or endoscopies (22.2 vs. 21.5%; p = 1.00) in the change and no change groups.

Secondary Outcomes

Total IBD-related health-care costs were higher in the change group (median GBP 7,912 vs. GBP 6,521; p < 0.0001). The extra costs related mainly to costs for a switch in medication from a biosimilar IFX to originator products of adalimumab, vedolizumab, or ustekinumab or an associated increase in day-case administration costs due to adjustments in IFX interval (median GBP 7,062 vs. GBP 6,012; p < 0.0001).

To account for recent reductions in costs of biosimilar IFX and a considerable reduction in costs for adalimumab due to the arrival of biosimilar adalimumab, we perform a further analysis with medication costs as applicable in 2020. At current medication prices, the median overall health-care cost for the change group would have been similar to the unchanged group (GBP 5,105 vs. GBP 5,060; p = 0.87). The cost of medication and medication administration were also similar (changed GBP 5,235 vs. unchanged GBP 4,603; p = 0.88).

Subgroup Analyses

Decision to Stop IFX (Subgroup I)

In the change group, 8 patients stopped IFX as they were in clinical remission despite unfavourable TDM (low trough levels and high ADAs). None were subsequently hospitalized or were switched to an alternative biologic. In the no change group who stopped IFX, one of 4 patients were hospitalized, and no patients were switched (p = 0.33 and p = 1.00, respectively). The median average 12-month cost for all IBD-related care was higher for the no change group (GBP 2,427.65) than the change group (GBP 607.25). This numerical difference did not reach statistical significance (p = 0.38). The drug and day-case administration costs were, however, higher in the no change group (GBP 1,214.10 vs. GBP 318.25; p = 0.048, Table 1).

Decision to Switch to a Different Biologic (Subgroup II)

Of 14 patients in the change group that were switched from IFX to a different biologic, none were subsequently hospitalized or switched to another biologic. By comparison, in the no change group, 1 of 2 patients was hospitalized, but none were subsequently switched to a different biologic (p = 0.13 and p = 1.00, respectively). In the change group, median average 12-month costs for all IBD-related care were lower than in the no change group (GBP 9,815.30 vs. GBP 13,175.00; p = 0.02). This difference was also seen for drug and day-case administration costs (GBP 9,548.00 change vs. GBP 11,181.10 no change; p = 0.02).

Adjusted IFX Dose or Infusion Interval (Subgroup III)

None of 25 patients with dose or interval adjusted IFX in the change group experienced a hospitalization or switch to another biologic. In contrast, 3 of 21 patients in the no change group with dose or interval adjusted IFX were hospitalized, but none had their biologic subsequently switched (p = 1.00). Total IBD-related health-care costs were lower in the change group than the no change group (GBP 7,220.00 vs. GBP 7,823.98; p < 0.001). Drug and day-case administration costs were, however, significantly higher for the change group than the no change group (GBP 7,168.80 vs. GBP 6,403.95; p < 0.001), due to the adjustments in IFX interval and dosing.

Continue at Same IFX Dose and Interval (Subgroup IV)

In the change group, 3 out of 6 patients were hospitalized and 1 patient required a subsequent switch to an alternative biologic. In the no change group, 10 out of 107 (9.3%) patients were hospitalized and 2 (1.9%) subsequently switched to an alternative biologic. The differences in hospitalization rates were lower in the no change group (p = 0.02). This effect was only seen in the analysis as by decisions implemented by clinicians. The 4 patients experiencing those events were continued on an unaltered dose of IFX as the MDT suggestions that incorporated the TDM results were not implemented by the treating clinician (Table 2). There was no statistical significance between the 2 groups for subsequent switch to a different biologic during the following 12 months (p = 0.15). Overall health-care costs in the change group were significantly higher than the no change group (GBP 8,486.05 vs. GBP 7,454.65; p < 0.001). Drug and day-case administration costs were also higher for the change group than the no change group (GBP 7,454.65 vs. GBP 6,001.60; p < 0.001).

Factors Associated with Inpatient Admission

To determine whether IFX levels and ADA levels at baseline were associated with the need for hospitalization, we compared median IFX trough levels (2.85 subsequent-

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Table 1. Patient outcomes on decision actually implemented by clinician's analysis

Decision changed by TDM (*n* = 53)	I-stop	II-switch	III-adjustment	IV-continue (no adjustment)
N	8	14	25	6
Hospitalizations	0	0	0	3
Subsequent switch	0	0	0	1
Total 12-month cost, median (range, 2016 prices)	607.25 (216–3,938)	9,815.30 (3,410.60–12,936.00)	7,220 (4,602.50–11,258.20)	8,486.05 (7,911.60–9,640.70)
Total 12-month cost, median (range, 2020 prices)	GBP 542 (GBP 216–3,155)	GBP 4,000 (GBP 1,862–12,936.00)	GBP 5,434 (GBP 3,689–8,335.00)	GBP 6,516 (GBP 5,613–8,352)
Average no. of scans per person	0.38	0.3	0.2	0.5
Average number of endoscopy per person	0	0.14	0.32	0.33
Drug + administration cost, median (range, 2016 prices)	318.25 (0–7,375.80)	9,548.00 (2,644.60–12,600)	7,166.80 (4,455.50–10,427.20)	7,454.65 (4,263.60–9,421.70)
Drug + administration cost, median (range, 2020 prices)	GBP 253 (0–GBP 2,770)	GBP 3,678 (GBP 1,096–12,600)	GBP 5,222 (GBP 3,542–7,504)	GBP 5,406 (GBP 3,324–6,286)
CD/UC/IBD-U	6/1/1	12/2/0	20/2/3	5/1/0
Decision unchanged by TDM (*n* = 134)	**I-stop**	**II-switch**	**III-adjustment**	**IV-continue**
N	4	2	21	107
Hospitalizations	1	1	3	10
Subsequent switch	0	0	0	2
Total 12-month cost, median (range, 2016 prices)	2,427.65 (72–9,053)	13,175.60 (11,568.10–14,783.10)	GBP 7,8238.98 (3,497.50–18,582.80)	6,371.80 (363–12,975.10)
Total 12-month cost, median (range, 2020 prices)	GBP 1,867 (GBP 72–8,896.40	GBP 5,272.50 (GBP 3,763–6,782)	GBP 5,626** (GBP 2,845–13,154)	GBP 5,048 (GBP 363–9,846)
Scans	0.25	0	0.43	0.31
Endoscopy	0	0.5	0.14	0.23
Drug + administration cost, median (range, 2016 prices)	1,214.10 (0–2,798.70)	11,181.10	6,403.95 (3,182.50–17,540.80)	6,001.60 (0–11,721.10)
Drug + administration cost, median (range, 2020 prices)	GBP 927 (GBP 0–2,094)	GBP 3,278 (GBP 3,180–3,376)	GBP 4,683** (GBP 2,530–12,112)	GBP 4,432 (GBP 0–6,902)
CD/UC/IBD-U	4/0/0	1/0/1	19/1/1	88/9/8

TDM, therapeutic drug monitoring.

Table 2. Outcomes on intention to treat as suggested by MDT analysis

Decision changed by TDM (*n* = 53)	I-stop	II-switch	III-adjustment	IV-continue (no adjustment)
N	8*	19	24	2
Hospitalizations	1	1	1	0
Subsequent switch	2	0	0	0
Total 12-month cost, median (range, 2016 prices)	GBP 386.00 (216.00–11,039.40)	GBP 9,744.50 (828.50–12,936)	GBP 6,984.85 (1,803.20–11,258.20)	GBP 6,697.65 (5,358–8,037.30)
Total 12-month cost, median (range, 2020 prices)	GBP 2,258 (GBP 216.00–6,972)	GBP 4,336 (GBP 698–12,936)	GBP 5,324 (GBP 1,490–8,335)	GBP 5,893 (GBP 5,393–6,393)
Average no. of scans per person	0.4	0.3	0.3	0.5
Average number of endoscopy per person	0.1	0.2	0.3	0.5
Drug + administration cost, median (range, 2016 prices)	GBP 0 (0–10,823.40)	GBP 9,489.10 (GBP 636.50–12,600)	GBP 6,552.15 (1,412.2–10,427)	GBP 6,124.65 (GBP 5,187–7,062.30)
Drug + administration cost, median (range, 2020 prices)	GBP 1,662 (GBP 0–5,562)	GBP 3,878 (GBP 506–12,600	GBP 5,115 (GBP 1,108–7,504)	GBP 5,320 (GBP 5,222–5,418)
CD/UC/IBD-U	6/1/1	16/3/0	20/3/1	1/0/1
Decision unchanged by TDM (n = 134)	**I-stop**	**II-switch**	**III-adjustment**	**IV-continue**
N	6	1	12	115
Hospitalizations (>24-h stay)	1	0	0	14
Subsequent switch	0	0	0	5
Total 12-month cost, median (range, 2016 prices)	GBP 5,107.00 (GBP 72–9,053.00)	GBP 9,789.10	GBP 7,265.83 (GBP 4,338.60–8,364.20)	GBP 6,397.35 (363–18,582)
Total 12-month cost, median (range, 2020 prices)	GBP 3,566 (GBP 72–8,896.40)	GBP 7,675	GBP 5,322 (GBP 3,399–6,485)	GBP 5,054 (363–13,154)
Scans	0.33	0	0	0.33
Endoscopy	0.17	1	0.08	0.25
Drug + administration cost, median (range, 2016 prices)	GBP 3,138.80 (0–5,152.80)	GBP 8,396.10	GBP 7,049.00 (GBP 4,263.6–8,086.40)	GBP 6,011.60 (858.80–17,540.80)
Drug + administration cost, median (range, 2020 prices)	GBP 1,854 (GBP 0–3,900)	GBP 6,282	GBP 5,211 (GBP 3,324–6,116)	GBP 4,432 (GBP 0–12,112)
CD/UC/IBD-U	5/1/0	1/0/0	12/0/0	96/9/10

MDT, multidisciplinary team; TDM, therapeutic drug monitoring.

ly hospitalized vs. 3.2 subsequently not hospitalized patients; $p = 0.74$) and median IFX ADAs (0 in those requiring admission vs. 0 not requiring admission; $p = 0.62$). Following implementation of the decisions of the virtual biologics clinic, median IFX levels during monitoring over the 12 months were 3.25 in those requiring admission and 3.2 in those not ($p = 0.49$). The median ADA level was 0 in those requiring admission versus 0 in those not ($p = 0.45$).

Discussion

The role of routine proactive TDM for all patients receiving IFX therapy, rather than those only experiencing secondary loss of response, is not fully established [8]. We have shown previously that knowledge of TDM results led to changes in decision-making at an annual assessment in a virtual biologics clinic in almost 30% of patients [13]. Our follow-up study confirms that decisions made based on the results of TDM provide clinically durable results without risking adverse patient outcomes. This should reassure clinicians who are concerned about altering clinical decisions based on the results of TDM for patients who are in clinical remission. In addition, we show that this was associated with a modest increase in healthcare expenditure.

Our study was performed when IFX was purchased at much reduced prices as a biosimilar product, but adalimumab, vedolizumab, and ustekinumab were all purchased at much higher originator prices. There may now be savings to be made, as at the time of our study, biosimilar IFX was used, but any patient switched to adalimumab would have been switched to the originator, with the associated full price costs. The introduction of biosimilar adalimumab in 2019 has drastically reduced the price, and so any patient switched to adalimumab would now have reduced drug expenditure, while during the 2016 study period, a switch to adalimumab would have increased drug-related costs. Indeed, when we performed an analysis based on drug prices from 2020, we found no difference in costs between changed and unchanged groups.

We have demonstrated the key clinical outcomes were no different between the change and no change groups overall. We used objective outcomes of inpatient admissions and a switch to another biologic therapy in a real-world study. This supports the use of routine IFX TDM to inform proactive clinical decisions, in addition to the established use of TDM in the setting of treatment failure. Our data show that in a subset of patients with unfavourable TDM results, and who are in clinical remission, IFX can be safely stopped without adverse outcomes or the need for a different biologic. In addition, in patients in clinical remission with high trough levels, we have been able to reduce dosing accordingly. Our current practice is to proactively measure TDM after completion of induction with the 4th infusion and annually thereafter. In addition, for any patient experiencing loss of response, we use TDM reactively.

Naturally, when looking at specific subgroups of patients, some differences were observed. We found a significant difference in hospitalization rates for the subgroup of patients with IFX continued at the current dose and interval. Here, patients with a decision altered by the results of TDM fared worse than those with decisions unchanged, albeit based on very small numbers. This effect was only seen in patients where the MDT suggestion to change treatment based on TDM was not implemented by the treating clinician.

The main strengths of our study include that we examined the whole cohort of IFX patients at our institution with proactive TDM. The cohort was also previously naïve to TDM as this only became available at our institution in 2016. Furthermore, we blinded the decision makers to the TDM results initially to reduce bias in decision-making.

There are a number of important limitations to our study. Firstly, this is a single centre experience, and clinical decision-making may vary from centre to centre. Secondly, the retrospective study design allowed for capture of all health-care encounters at our institution, but we could not collect any encounters that may have occurred outside our institution. We also did not record encounters with primary care. Thirdly, in a rapidly changing health-care market, drug-related costs change continually, with variations between different regions and countries. These results may therefore not be universally applicable. Finally, our study cannot establish whether TDM-based decision-making in virtual biologics clinic is superior to the previous, clinically based driven, standard of care. In our centre, a comparator group, who were not exposed to TDM, did not exist. We instead chose to compare outcomes with the no change group. We would have expected that this group of patients would do particularly well as the group consisted predominantly of patients with a combination of favourable TDM, a favourable response to IFX, and a clinical indication to continue IFX. If anything, this group would be expected to have better, not worse, outcomes than the change group. However, in order to determine whether

TDM-based management is superior to the previous standard of care a clinical trial comparing previous standard of care management with proactive TDM would have to be much larger than the TACIT study to have sufficient power to detect clinically meaningful differences in outcome [9]. Given the resources required to perform such a study, it is doubtful such a study would ever be performed. In conclusion, our study demonstrates that the use of results of TDM, in conjunction with routine information such as biochemistry, imaging, endoscopic, and clinical assessment, to make decisions concerning whether to adjust or stop IFX therapy in patients with IBD can safely influence management, without negatively affecting patient outcomes, such as increased hospitalization or requirement for a further switch of biologic treatment.

Statement of Ethics

The study was conducted as a retrospective clinical audit. Relevant clinical audit authorization was obtained. Due to the nature of this pragmatic service evaluation study, research ethics committee approval and informed consent were not required [15].

Conflict of Interest Statement

C.P.S. has received unrestricted research grants from Warner Chilcott, Janssen, and AbbVie, has provided consultancy to Warner Chilcott, Dr. Falk, AbbVie, Takeda, Fresenius Kabi, and Janssen, and had speaker arrangements with Warner Chilcott, Dr. Falk, AbbVie, MSD, Pfizer, and Takeda. T.A. has received unrestricted educational grants, consultancy fees, speaker fees, and support to attend conferences from AbbVie, MSD, NAPP, Pfizer, Janssen, and Takeda. P.J.H. has received speaker fees from AbbVie, Ferring, MSD, and Takeda, and fees for advisory boards from Warner Chilcott, Dr. Falk, AbbVie, Takeda, and Otsuka. D.J.G. has received speaker fees from Takeda and AbbVie. All other authors declare no conflict of interest.

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Author Contributions

C.P.S., A.O.C., and P.J.H. designed the study. R.S. led the data collection. All authors contributed to data collection and interpretation of results. R.S. and C.P.S. analysed the data. R.S. wrote the draft manuscript. All other authors critically reviewed the manuscript.

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